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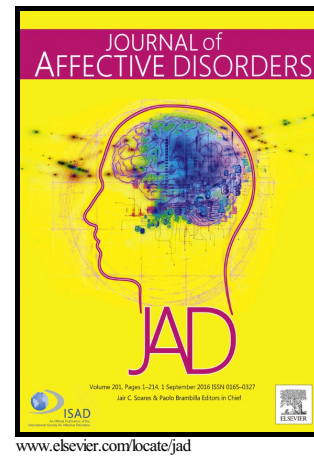
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Apathy in Early and Late-life depression

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Abstract

Background: Late-life depression is thought to differ in clinical presentation from early-life depression. Particularly, late-life depression is considered to be more characterized by apathy than is early-life depression. Lacking convincing evidence, this study examines the presence and associated socio-demographic/clinical characteristics of apathy in older compared to younger depressed persons.

Methods: This cross-sectional study used data from two naturalistic cohort studies, i.e. the Netherlands Study of Depression in Older Persons (NESDO) and the Netherlands Study of Depression and Anxiety (NESDA). These studies included 605

persons (aged 18-93 years) with a major depressive disorder, divided into 217 early-life (<60 years) and 388 late-life (≥ 60 years) depressed persons. Apathy was considered present if a score of ≥ 14 on the Apathy Scale.

Results: Apathy was strongly associated with age: it was more frequently present in persons with late-life depression (74.5%) than in those with early-life depression (53.5%). Independent of age, the following characteristics were associated with the presence of apathy: male gender, low education, use of benzodiazepines, chronic diseases, and more severe depression. Of all potential risk factors, only former and current smoking was associated with the presence of apathy in older depressed persons but not in younger depressed persons (p-value for age interaction=0.01).

Limitations: No causal relationships can be drawn due to the cross-sectional design of the study.

Conclusions: In depressed individuals, clinically relevant apathy was more frequently present in older compared to younger persons. Both age groups showed largely the same associated risk factors. Apathy was independently associated with older age, male gender and more severe depression.

Introduction

Depression is one of the most prevalent psychiatric disorders, affecting 5-8% of the population worldwide (Shahpesandy, 2005). It is often stated that depressive symptoms differ between younger and older depressed persons. For example, studies have demonstrated that late-life compared to early-life depressed persons show increased psychomotor retardation, decreased activity (Brodaty et al., 1997; Brodaty et al., 1991; Shahpesandy, 2005) and show less mood symptoms (i.e. feelings of guilt) (Hegeman et al., 2012; Lyness et al., 1995; Shahpesandy, 2005; Yates et al., 2004), all of which resemble symptoms of apathy. Therefore, apathy

may be considered to be a characteristic feature of especially late-life depression (Shahpesandy, 2005). However, apathy (as a clinically relevant syndrome) can be diagnosed when a cluster of clinical features is present (consisting of a loss of motivation, interest and concern) resulting in decreased goal-directed behavior, emotional responsiveness and cognitive activity.

Distinguishing apathy (as a syndrome) from depression can be a major challenge due to an overlap in symptoms, e.g. loss of interest, which is also found in anhedonia. Although both apathy and anhedonia indicate lack/decrease of interest, the latter presents a state of decreased experienced pleasure in activities, whilst apathy is characterized by a lack of primary motivation and affective dullness. (Kaji and Hirata, 2011; Kirsch-Darrow et al., 2011)

Studies in different populations show that the following risk factors are associated with apathy as a clinically relevant syndrome in old age: vascular disease, excessive use of alcohol, use of benzodiazepines, smoking and the presence of chronic diseases (Adams, 2001; Clarke et al., 2010; Lyvers et al., 2013; Lyvers et al., 2014; Maas et al., 2009; Moselhy et al., 2001; Onyike et al., 2007; Semprini et al., 2012; van der Mast et al., 2008; van Duijn et al., 2010; Winhusen et al., 2013). The few studies on clinically relevant apathy in depressed persons have focused mainly on older populations. In one cross-sectional study in depressed older persons: i) clinically relevant apathy was associated with severity of depression; whereas, longitudinally: ii) impaired cognitive function at baseline predicted incident apathy, and iii) more severe apathy at baseline predicted persistence of apathy and depression, whereas iv) remitted apathy was associated with less use of benzodiazepines (Groeneweg-Koolhoven et al., 2016). In addition, no association was found between apathy and the use of antidepressants or presence of

cardiovascular diseases (Groeneweg-Koolhoven et al., 2016). Further, apathy appeared to be a predictor of poor response to antidepressant treatment (Levkovitz et al., 2011; Wongpakaran et al., 2007), chronicity of depression (Groeneweg-Koolhoven et al., 2016; Lavretsky et al., 1999), a poor prognosis, and increased overall mortality rates (Lavretsky et al., 2010; Yasuda et al., 2002). Improved treatment of clinically relevant apathy within a depressed group would ameliorate the prognosis. Therefore, it is of clinical relevance to have better understanding of the position of clinically relevant apathy in depressed persons (Brodaty et al., 1997; Brodaty et al., 1991; Shahpesandy, 2005).

Systematic studies measuring the same apathy concept in late-life and early-life depression are lacking. Consequently, it is unknown whether apathy as a distinct and clinically relevant syndrome is indeed much less present in depressed younger persons than in depressed older persons; and, if so, whether apathy has similar associating sociodemographic and clinical correlates in older depressed persons compared to younger depressed persons.

Therefore, the present study examines whether: the prevalence of apathy (as a distinct clinically relevant syndrome) differs between late-life and early-life depression and whether certain late-life comorbidities (e.g. chronic diseases, atherosclerosis, severity of depression, use of alcohol, use of benzodiazepines and smoking) partly explain such an age difference. In addition, we examined whether the found determinants of apathy are more important (moderating) in late-life than in early-life.

Methods

Study design

This cross-sectional study is part of the Netherlands Study of Depression in Older persons (NESDO) and the Netherlands Study of Depression and Anxiety (NESDA). Both are multi-site naturalistic, prospective cohort studies designed to examine the psychosocial, neurobiological and clinical determinants, course and consequences of depressive disorders. All participants were recruited from general practices, mental healthcare organizations, and university medical centers. Exclusion criteria were: a diagnosis of dementia or a Mini Mental State Examination score (MMSE) ≤ 18 (only NESDO), the presence of another primary psychiatric disorder (e.g. psychotic or bipolar disorder), and insufficient mastery of the Dutch language.

The design of these studies are largely similar in scope and are described in earlier reports (Comijs et al., 2011; Penninx et al., 2008). Apathy was measured in both waves of NESDO as well as in the 6 year follow-up of NESDA. The main differences between the two studies are the inclusion of both depression and anxiety disorders in the NESDA study, whereas the NESDO study included persons suffering from depression alone, and also included inpatients (n=26).

For the current analysis we used i) baseline data of the NESDO participants (age range 60-93 years) but excluding their inpatients, and ii) the 6-year follow-up data from the NESDA study (age range 24-71 years). From these studies, we included only the 605 participants who, irrespective of age of onset of depression, had a current (6-month recency) diagnosis of major depressive disorder (217 early-life, 388 late-life) according to the DSM-IV criteria (American Psychiatric Association) as assessed with the Composite International Diagnostic Interview; CIDI; WHO version 2.1; life-time version) (Wittchen et al., 1991) and who had completed Apathy Scale

scores. Early-life (< 60 years) and late-life (\geq 60 years) depression was defined using a cut-off age of 60 years, which is mostly commonly used (Brodaty et al., 2005a; Brodaty et al., 1991; Gournellis et al., 2011).

Both study protocols were approved by the Ethical Review Boards of all the participating centers. Before enrollment all participants gave written informed consent.

Measures

Assessment of apathy

Apathy was assessed with the Apathy Scale, used as a self-report questionnaire that has demonstrated good psychometric properties (Pedersen et al., 2012; Starkstein et al., 1992). The Apathy Scale consists of 14 items with four possible answers ranging from 0-3 (maximum 42) points (Pedersen et al., 2012; Starkstein et al., 1992); higher scores indicate more severe apathy (Starkstein et al., 1992). In different clinical populations, a cut-off score of 14 showed a moderate sensitivity and a high specificity for the presence of clinically relevant apathy (Pedersen et al., 2012; Starkstein et al., 1993; Starkstein et al., 1992; Starkstein et al., 2001).

Assessment of presence and severity of depression

The presence of a depressive disorder in the 6 months before the measurement was assessed with the CIDI (WHO version 2.1; life-time version) (Wittchen et al., 1991).

The severity of depressive symptoms was assessed using the 30-item self-report Inventory of Depressive Symptomatology (IDS-SR) (Rush et al., 1996) with higher scores indicating more severe depression.

Assessment of other characteristics

For all participants, information was obtained on gender, age, and education.

Education was divided into three levels: basic (0-8 years), intermediate (9-14 years), and high (>15 years) (Prins et al., 2010).

For the assessment of chronic diseases, a self-rating questionnaire was used asking the participants whether they currently or previously had any of the following chronic diseases or disease events: cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, lung disease, osteoarthritis or cancer, or any other disease (Comijs et al., 2011; Penninx et al., 2008). The accuracy of self-report of these diseases has shown to be adequate and independent of cognitive impairment compared to data obtained from general practitioners (Kriegsman et al., 1996).

The self-reported use of benzodiazepines (on a daily basis only), i.e. anxiolytics and hypnotics, was classified using the Anatomical Therapeutic Chemical Classification system (Norwegian, 2011). The number of alcoholic drinks a day was assessed with the Alcohol use Disorders Identification Test (AUDIT) (Babor et al., 1989).

Smoking status was defined as non-smoker, former smoker or current smoker.

The ankle/brachial index (ABI) was used as an indicator of peripheral atherosclerosis. Doppler assessment (with an electronic Omron sphygmomanometer) of ankle and arm systolic blood pressure enabled to calculate the ABI (Newman et al., 1993).

Statistical analysis

Data are presented as numbers with percentages, medians with interquartile ranges (IQR), or means with standard deviations (SD), where appropriate. Using univariate analyses, persons with late-life (≥ 60 years) depression and early-life (< 60 years) depression were compared with regard to the presence and severity of apathy,

severity of depression, chronic diseases, atherosclerosis, use of alcohol, use of benzodiazepines, and smoking.

To further examine correlates of clinically relevant apathy in late-life and early-life depression, logistic and multivariable regression analyses were performed in the total group of depressed persons adjusted for severity of depression. Additionally, to investigate whether the association between apathy and late-life depression is moderated by specific late-life comorbidities, both an interaction term age*potential risk factor and an ELD/LLD*potential risk factor were studied in the regression model that was adjusted for severity of depression. ~~and age~~. We present the results of age as a continuous instead of a dichotomous (early-life versus late-life) measure, since this yields more sensitivity. The continuous variable age was centered to avoid multicollinearity. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. A p-value < 0.05 was considered statistically significant.

~~To examine whether the association between apathy and late-life depression is moderated by specific late-life comorbidities an interaction term age centered * potential risk factor was studied in the regression model that was adjusted for severity of depression and age.~~

For sensitivity analysis, all analyses were repeated using age as a continuous variable in the interaction term and using cut-off scores of 13, 15 and 18 on the Apathy Scale (Kant et al., 1998). Statistical analyses were performed with SPSS 22.0 (IBM for Windows).

Results

Table 1 presents the characteristics of early-life and late-life depressed persons. The two groups with early-life depression (mean age 43.6, SD 9.8 years) and late-life depression (mean age 69.7, SD 7.3 years) showed no significant difference in gender (71.4% and 66% female gender, respectively).

Compared to early-life depression, persons with late-life depression had a lower educational level, more chronic diseases, more often used benzodiazepines, were more often former smokers, used more alcohol, and had a lower mean ABI.

Furthermore, in late-life depressed persons, clinically relevant apathy according to an Apathy Scale score ≥ 14 was significantly more often present (also when corrected for severity of depression) and their mean Apathy Scale score and IDS score were higher, compared to early-life depressed persons, regardless of age of onset of depression in persons with late-life depression.

< Table 1 >

In the whole group of depressed persons, higher severity of depression was associated with the presence of apathy. When, corrected for severity of depression, the following were also associated with the presence of apathy: male gender, lower education, more chronic diseases, more use of benzodiazepines (Table 2).

<Table 2>

Of all eight individual interaction terms, only 'age x smoking' and 'age x ABI' were associated with the presence of apathy. After stratification for early-life and late-life depression, older depressed persons with apathy were more often former and current

smokers compared to older depressed persons without apathy (OR=1.74, 95% CI=0.99-3.03, $p=0.05$ and OR=2.05, 95% CI=1.08-3.89, $p=0.03$, respectively) (supplementary table, not shown). Younger depressed persons with apathy did not differ in their smoking habits from those without apathy (OR=0.73, 95% CI=0.37-1.44, $p=0.4$ and OR=0.66, 95% CI=0.36-1.24, $p=0.7$, respectively). However, both older and younger depressed persons with apathy had no difference in ABI compared with those without apathy (supplementary table, not shown).

Table 3 shows that, among the whole group of depressed persons, age (OR=1.0, 95% CI=1.01-1.04, $p<0.001$), male gender (OR=0.5, 95% CI=0.35-0.80, $p=0.003$) and higher IDS (OR=1.1, 95% CI=1.04-1.06, $p<0.001$) scores were independent correlates of apathy.

All analyses were repeated with different cut-off scores on the Apathy Scale (i.e. 13, 15, and 18), which yielded similar results.

Discussion

In this study, apathy as a clinically relevant syndrome, was more often present in older depressed persons (269/363; 75%) compared to younger depressed persons (116/217; 54%) and was also more severe in the older group, independent of the severity of depression.

In the whole group of depressed persons, apathy was associated with male gender, lower education, more frequent use of benzodiazepines, more chronic diseases and more severe depression. In older depressed persons, smoking was associated with the presence of clinically relevant apathy, which was not the case in younger

depressed persons. In the whole group of depressed persons, apathy was independently associated with older age, male gender and more severe depression. The presence of clinically relevant apathy in depressed older persons is in accordance with other studies (Groeneweg-Koolhoven et al., 2014; Lampe and Heeren, 2004; Marin et al., 1994; Wongpakaran et al., 2007). It is known that apathy, as assessed with the items 'psychomotor retardation' and 'decreased activity' of the Hamilton Rating Scale for Depression is often present in younger persons suffering from depression, although less often than in older depressed persons (Brodaty et al., 1997; Brodaty et al., 1991; Shahpesandy, 2005). The prevalence and associating factors of apathy as a clinically relevant syndrome, operationalized as a cluster of clinical features according to the Apathy Scale, have not yet been examined before in younger depressed persons. The present study shows that, in more than half of the younger depressed persons, clinically relevant apathy was present; although, significantly less than in the older depressed group.

In late-life depression, the presence and severity of apathy is known for its negative influence on the prognosis and treatment response of depression (Levkovitz et al., 2011; Mitchell and Subramaniam, 2005; Uher et al., 2012; Vinkers et al., 2004). However, it is unknown whether clinically relevant apathy in younger depressed persons has a similar negative influence on the course of depression.

Apart from smoking, no differences in associating factors for apathy were found in early-life and late-life depression. Male gender, lower education, use of benzodiazepines, presence of chronic diseases, and a higher severity of depression are all reported to be associated with apathy in older depressed persons (Brodaty et al., 2010; Groeneweg-Koolhoven, 2015; Maas et al., 2009). However, in the present study, only (former and current) smoking was specifically related to the presence of

apathy in late-life depression but not in early-life depression. This finding is partly in contrast with an earlier study reporting that current smokers, compared to long-term ex-smokers and never smokers (aged 19-58 years), scored significantly higher on the three-item subscale for apathy of the Frontal System Behavior Scale (Lyvers et al., 2014). However, this subscale only scores some apathetic-type symptoms, rather than clinically relevant apathy as a syndrome according to the Apathy Scale. Cross-sectional studies in community-based older persons and stroke patients showed no association between current smoking and the presence of apathy in older persons (Brodaty et al., 2005b; Yasuda et al., 2002). However, no studies have examined the long-term effects of smoking (duration of smoking in years and total cigarettes a day) on motivation.

In the present study, the ABI (as a measure for generalized atherosclerosis) was not associated with the presence of apathy in the separate age groups. This is in contrast to studies among community-based populations reporting that the presence of cerebrovascular disease and risk factors are associated with the presence of apathy (Ligthart et al., 2012; van der Mast et al., 2008). However, other studies among depressed older persons failed to show this association, probably due to different populations and the use of a more validated measurement to assess apathy (Groeneweg-Koolhoven et al., 2016; Groeneweg-Koolhoven et al., 2015). Also, age, male gender and severity of depression were independent correlates of apathy in the depressed group; this is in accordance with earlier reports (Adams, 2001; Clarke et al., 2010; Mehta et al., 2008; Onyike et al., 2007; van der Mast et al., 2008).

The present study is the first to compare the presence, severity and correlates of apathy in early versus late-life depressed persons in a large sample. Earlier we examined the presence, correlates and predictors of apathy in depressed older

persons from the NESDO study. For this study we had the opportunity to enlarge the study population with data from the NEDA study, to examine differences between younger and older depressed persons concerning the presence and correlates of apathy. An important strength of the present study is that both depression and apathy were assessed using established validated measures.

Some limitations also need to be addressed. First, we cannot conclude whether depression, in the course of the time, is more associated with the presence of apathy, since this study has a cross-sectional design. Second, patients were recruited from primary care and from outpatient secondary care clinics, whereas inpatients from the NESDO cohort were excluded; this limits the generalizability of the results to more severe depressed inpatients. Third, the Apathy Scale was a self-report measure, which could have resulted in subjective underscore related the presence of apathy. Further, scores on the Apathy Scale were dichotomized in accordance with the results from psychometric studies in Parkinson and Alzheimer's disease using a cut-off score of 14 (Pedersen et al., 2012; Starkstein et al., 1992), which may have led to under- or overestimation of the presence of clinically relevant apathy. However, additional post-hoc analyses using different cut-off scores of the Apathy Scale yielded similar results regarding the presence and correlates of apathy in older compared to younger depressed persons. Fourth, we had only partial information on cognitive functioning, since the MMSE was conducted only in the NESDO cohort. In addition, in NESDO, we excluded individuals with (according to their clinician) a suspected diagnosis of dementia. Nevertheless, we may have included older persons with early dementia, because it is difficult to diagnose dementia when an individual is depressed. Therefore, we performed sensitivity analyses using a cut-off score of < 24 on the MMSE thereby excluding a total of 16 older persons; however these analyses

yielded similar results. Fifth, we didn't compare the results with a non-depressed control group which limits generalisability of the results. Last, although the same measures were used to assess depression according to DSM-IV criteria and apathy in both cohorts, and inpatients from the NESDO study were excluded, differences between the two cohort studies might explain the higher presence of apathy found in the late-life depressed individuals. Also, since the recruitment of depressed persons from the NESDA study, but not the NESDO study, was also from the general population, this might have resulted in the inclusion of less severe depressed persons in the early-life depression group. In addition, global cognitive functioning was not assessed in the NESDA study, resulting in the inclusion of persons with a cognitive decline in the late-life depressed group.

In clinical setting, differentiating apathy from depression can be troublesome due to overlapping symptoms, such as diminished interest, activity and energy. However, apathy lacks mood-related symptoms and is primarily a motivational disorder showing a decrease in goal-directed behaviour, emotional blunting, indifference and loss of initiative (Leontjevas et al., 2013; Levy et al., 1998; Marin et al., 1993).

Recognizing apathy as a clinically relevant syndrome accompanying a depressive disorder is essential, since apathy predicts poor response of depressive symptoms to treatment, chronicity of depression and functional impairment (Groeneweg-Koolhoven et al., 2016; Levkovitz et al., 2011; Yuen et al., 2015).

In conclusion, our findings show that the presence and severity of clinically relevant apathy was significantly less in early-life depressed persons compared to late-life depressed persons showing that both older and younger depressed persons had largely the same associating risk factors, with the exception of smoking which was associated with the presence of apathy in older depressed persons only.

Furthermore, in the entire study population age, male gender and severity of depression were independently associated with the presence of apathy in the entire study population.

Whether apathy as a clinically relevant syndrome in early-life depression has the same negative outcomes as in late-life depression remains unknown. Longitudinal studies are necessary to clarify the position and implications of apathy in early-life depressed persons on the long term.

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The funders had no role in the study design or in the collection, analysis, interpretation and reporting of data. Further, the authors have no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

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Ethical Statement

The authors declare that no human or animal experimentation was conducted for this work.

References

- Adams, K.B., 2001. Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *The Gerontologist* 41, 768-777.
- Babor, T.F., Kranzler, H.R., Lauerman, R.J., 1989. Early detection of harmful alcohol consumption: comparison of clinical, laboratory, and self-report screening procedures. *Addictive behaviors* 14, 139-157.
- Brodaty, H., Altendorf, A., Withall, A., Sachdev, P., 2010. Do people become more apathetic as they grow older? A longitudinal study in healthy individuals. *International psychogeriatrics / IPA* 22, 426-436.
- Brodaty, H., Cullen, B., Thompson, C., Mitchell, P., Parker, G., Wilhelm, K., Austin, M.P., Malhi, G., 2005a. Age and gender in the phenomenology of depression. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 13,

589-596.

- Brodaty, H., Luscombe, G., Parker, G., Wilhelm, K., Hickie, I., Austin, M.P., Mitchell, P., 1997. Increased rate of psychosis and psychomotor change in depression with age. *Psychological medicine* 27, 1205-1213.
- Brodaty, H., Peters, K., Boyce, P., Hickie, I., Parker, G., Mitchell, P., Wilhelm, K., 1991. Age and depression. *Journal of affective disorders* 23, 137-149.
- Brodaty, H., Sachdev, P.S., Withall, A., Altendorf, A., Valenzuela, M.J., Lorentz, L., 2005b. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke - the Sydney Stroke Study. *Psychological medicine* 35, 1707-1716.
- Clarke, D.E., Ko, J.Y., Lyketsos, C., Rebok, G.W., Eaton, W.W., 2010. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. *International psychogeriatrics / IPA* 22, 819-829.
- Comijs, H.C., van Marwijk, H.W., van der Mast, R.C., Naarding, P., Oude Voshaar, R.C., Beekman, A.T., Boshuisen, M., Dekker, J., Kok, R., de Waal, M.W., Penninx, B.W., Stek, M.L., Smit, J.H., 2011. The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC research notes* 4, 524.
- Gournellis, R., Oulis, P., Rizos, E., Chourdaki, E., Gouzaris, A., Lykouras, L., 2011. Clinical correlates of age of onset in psychotic depression. *Archives of gerontology and geriatrics* 52, 94-98.
- Groeneweg-Koolhoven, I., Comijs, H.C., Naarding, P., de Waal, M.W., van der Mast, R.C., 2016. Apathy in Older Persons With Depression: Course and Predictors: The NESDO Study. *Journal of geriatric psychiatry and neurology* 29, 178-186.
- Groeneweg-Koolhoven, I., de Waal, M.W., van der Weele, G.M., Gussekloo, J., van der Mast, R.C., 2014. Quality of life in community-dwelling older persons with apathy. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 22, 186-194.
- Groeneweg-Koolhoven, I.C., Hannie C; Naarding, Paul; de Waal, Margot MW; van der Mast, Roos 2015. Presence and correlates of apathy in non-demented depressed and non-depressed older persons. . *Eur. J. Psychiat.* 29, 119-130.
- Hegeman, J.M., Kok, R.M., van der Mast, R.C., Giltay, E.J., 2012. Phenomenology of depression in older compared with younger adults: meta-analysis. *The British journal of psychiatry : the journal of mental science* 200, 275-281.
- Kaji, Y., Hirata, K., 2011. Apathy and anhedonia in Parkinson's disease. *ISRN neurology* 219427.
- Kant, R., Duffy, J.D., Pivovarnik, A., 1998. Prevalence of apathy following head injury. *Brain injury* 12, 87-92.
- Kirsch-Darrow, L., Marsiske, M., Okun, M.S., Bauer, R., Bowers, D., 2011. Apathy and depression: separate factors in Parkinson's disease. *Journal of the International Neuropsychological Society : JINS* 17, 1058-1066.
- Kriegsman, D.M., Penninx, B.W., van Eijk, J.T., Boeke, A.J., Deeg, D.J., 1996. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of clinical epidemiology* 49, 1407-1417.
- Lampe, I.K., Heeren, T.J., 2004. Is apathy in late-life depressive illness related to age-at-onset, cognitive function or vascular risk? *International psychogeriatrics / IPA* 16, 481-486.
- Lavretsky, H., Lesser, I.M., Wohl, M., Miller, B.L., Mehringer, C.M., 1999. Clinical and neuroradiologic features associated with chronicity in late-life depression. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 7, 309-316.
- Lavretsky, H., Zheng, L., Weiner, M.W., Mungas, D., Reed, B., Kramer, J.H., Jagust, W., Chui, H., Mack, W.J., 2010. Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *The American journal of psychiatry* 167, 589-597.
- Leontjevas, R., Teerenstra, S., Smalbrugge, M., Vernooij-Dassen, M.J., Bohlmeijer, E.T., Gerritsen, D.L., Koopmans, R.T., 2013. More insight into the concept of apathy: a multidisciplinary

- depression management program has different effects on depressive symptoms and apathy in nursing homes. *International psychogeriatrics / IPA* 25, 1941-1952.
- Levkovitz, Y., Sheer, A., Harel, E.V., Katz, L.N., Most, D., Zangen, A., Isserles, M., 2011. Differential effects of deep TMS of the prefrontal cortex on apathy and depression. *Brain stimulation* 4, 266-274.
- Levy, M.L., Cummings, J.L., Fairbanks, L.A., Masterman, D., Miller, B.L., Craig, A.H., Paulsen, J.S., Litvan, I., 1998. Apathy is not depression. *The Journal of neuropsychiatry and clinical neurosciences* 10, 314-319.
- Ligthart, S.A., Richard, E., Fransen, N.L., Eurelings, L.S., Beem, L., Eikelenboom, P., van Gool, W.A., Moll van Charante, E.P., 2012. Association of vascular factors with apathy in community-dwelling elderly individuals. *Archives of general psychiatry* 69, 636-642.
- Lyness, J.M., Cox, C., Curry, J., Conwell, Y., King, D.A., Caine, E.D., 1995. Older age and the underreporting of depressive symptoms. *Journal of the American Geriatrics Society* 43, 216-221.
- Lyvers, M., Carlopio, C., Bothma, V., Edwards, M.S., 2013. Mood, mood regulation expectancies and frontal systems functioning in current smokers versus never-smokers in China and Australia. *Addictive behaviors* 38, 2741-2750.
- Lyvers, M., Carlopio, C., Vicole Bothma, H., Edwards, M.S., 2014. Mood, mood regulation, and frontal systems functioning in current smokers, long-term abstinent ex-smokers, and never-smokers. *Journal of psychoactive drugs* 46, 133-139.
- Maas, D.W., van der Mast, R.C., de Craen, A.J., 2009. Increased C-reactive protein is not associated with apathy: the Leiden 85-Plus Study. *International journal of geriatric psychiatry* 24, 1177-1184.
- Marin, R.S., Firinciogullari, S., Biedrzycki, R.C., 1993. The sources of convergence between measures of apathy and depression. *Journal of affective disorders* 28, 117-124.
- Marin, R.S., Firinciogullari, S., Biedrzycki, R.C., 1994. Group differences in the relationship between apathy and depression. *The Journal of nervous and mental disease* 182, 235-239.
- Mehta, M., Whyte, E., Lenze, E., Hardy, S., Roumani, Y., Subashan, P., Huang, W., Studenski, S., 2008. Depressive symptoms in late life: associations with apathy, resilience and disability vary between young-old and old-old. *International journal of geriatric psychiatry* 23, 238-243.
- Mitchell, A.J., Subramaniam, H., 2005. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *The American journal of psychiatry* 162, 1588-1601.
- Moselhy, H.F., Georgiou, G., Kahn, A., 2001. Frontal lobe changes in alcoholism: a review of the literature. *Alcohol and alcoholism (Oxford, Oxfordshire)* 36, 357-368.
- Newman, A.B., Siscovick, D.S., Manolio, T.A., Polak, J., Fried, L.P., Borhani, N.O., Wolfson, S.K., 1993. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation* 88, 837-845.
- Norwegian, institue of public health, 2011. Anatomical Therapeutic Chemical Classification with used daydoses. WHO Collaborating Centre for Drugs Statistics.
- Onyike, C.U., Sheppard, J.M., Tschanz, J.T., Norton, M.C., Green, R.C., Steinberg, M., Welsh-Bohmer, K.A., Breitner, J.C., Lyketsos, C.G., 2007. Epidemiology of apathy in older adults: the Cache County Study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 15, 365-375.
- Pedersen, K.F., Alves, G., Larsen, J.P., Tysnes, O.B., Moller, S.G., Bronnick, K., 2012. Psychometric properties of the Starkstein Apathy Scale in patients with early untreated Parkinson disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 20, 142-148.
- Penninx, B.W., Beekman, A.T., Smit, J.H., Zitman, F.G., Nolen, W.A., Spinhoven, P., Cuijpers, P., De Jong, P.J., Van Marwijk, H.W., Assendelft, W.J., Van Der Meer, K., Verhaak, P., Wensing, M., De Graaf, R., Hoogendijk, W.J., Ormel, J., Van Dyck, R., 2008. The Netherlands Study of Depression and Anxiety (NESDA): rationale, objectives and methods. *International journal of*

- methods in psychiatric research 17, 121-140.
- Prins, M.A., Verhaak, P.F., Smolders, M., Laurant, M.G., van der Meer, K., Spreeuwenberg, P., van Marwijk, H.W., Penninx, B.W., Bensing, J.M., 2010. Patient factors associated with guideline-concordant treatment of anxiety and depression in primary care. *Journal of general internal medicine* 25, 648-655.
- Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological medicine* 26, 477-486.
- Semprini, R., Lubrano, A., Misaggi, G., Martorana, A., 2012. Apathy as marker of frail status. *Journal of aging research* 2012, 436251.
- Shahpesandy, H., 2005. Different manifestation of depressive disorder in the elderly. *Neuroendocrinology letters* 26, 691-695.
- Starkstein, S.E., Fedoroff, J.P., Price, T.R., Leiguarda, R., Robinson, R.G., 1993. Apathy following cerebrovascular lesions. *Stroke; a journal of cerebral circulation* 24, 1625-1630.
- Starkstein, S.E., Mayberg, H.S., Preziosi, T.J., Andrezejewski, P., Leiguarda, R., Robinson, R.G., 1992. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *The Journal of neuropsychiatry and clinical neurosciences* 4, 134-139.
- Starkstein, S.E., Petracca, G., Chemerinski, E., Kremer, J., 2001. Syndromic validity of apathy in Alzheimer's disease. *The American journal of psychiatry* 158, 872-877.
- Uher, R., Perlis, R.H., Henigsberg, N., Zobel, A., Rietschel, M., Mors, O., Hauser, J., Dernovsek, M.Z., Souery, D., Bajs, M., Maier, W., Aitchison, K.J., Farmer, A., McGuffin, P., 2012. Depression symptom dimensions as predictors of antidepressant treatment outcome: replicable evidence for interest-activity symptoms. *Psychological medicine* 42, 967-980.
- van der Mast, R.C., Vinkers, D.J., Stek, M.L., Bek, M.C., Westendorp, R.G., Gussekloo, J., de Craen, A.J., 2008. Vascular disease and apathy in old age. The Leiden 85-Plus Study. *International journal of geriatric psychiatry* 23, 266-271.
- van Duijn, E., Reedeker, N., Giltay, E.J., Roos, R.A., van der Mast, R.C., 2010. Correlates of apathy in Huntington's disease. *The Journal of neuropsychiatry and clinical neurosciences* 22, 287-294.
- Vinkers, D.J., Stek, M.L., Gussekloo, J., Van Der Mast, R.C., Westendorp, R.G., 2004. Does depression in old age increase only cardiovascular mortality? The Leiden 85-plus Study. *International journal of geriatric psychiatry* 19, 852-857.
- Winhusen, T.M., Somoza, E.C., Lewis, D.F., Kropp, F.B., Horigian, V.E., Adinoff, B., 2013. Frontal systems deficits in stimulant-dependent patients: evidence of pre-illness dysfunction and relationship to treatment response. *Drug and alcohol dependence* 127, 94-100.
- Wittchen, H.U., Robins, L.N., Cottler, L.B., Sartorius, N., Burke, J.D., Regier, D., 1991. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British journal of psychiatry : the journal of mental science* 159, 645-653, 658.
- Wongpakaran, N., van Reekum, R., Wongpakaran, T., Clarke, D., 2007. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Annals of general psychiatry* 6, 7.
- Yasuda, N., Mino, Y., Koda, S., Ohara, H., 2002. The differential influence of distinct clusters of psychiatric symptoms, as assessed by the general health questionnaire, on cause of death in older persons living in a rural community of Japan. *Journal of the American Geriatrics Society* 50, 313-320.
- Yates, W.R., Mitchell, J., Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Warden, D., Hauger, R.B., Fava, M., Gaynes, B.N., Husain, M.M., Bryan, C., 2004. Clinical features of depressed outpatients with and without co-occurring general medical conditions in STAR*D. *General hospital psychiatry* 26, 421-429.
- Yuen, G.S., Bhutani, S., Lucas, B.J., Gunning, F.M., AbdelMalak, B., Seirup, J.K., Klimstra, S.A., Alexopoulos, G.S., 2015. Apathy in Late-Life Depression: Common, Persistent, and Disabling. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry* 23, 488-494.

Table 1

Sociodemographic and clinical characteristics of early-life depression and late-life depression.

	Type of depression				p-value
	Early-life (18-60 years) n=217		Late-life (≥60 years) n=363		
Demographic characteristics					
Age in years, mean (SD)	43.6	(9.8)	69.7	(7.3)	<0.001**
Female gender, n (%)	155	(71.4)	240	(66)	0.2*
Education, n (%)					<0.001*
Basic	12	(5.5)	75	(20.7)	
Intermediate	112	(51.6)	202	(55.6)	
High	93	(42.9)	86	(23.7)	
Clinical characteristics					
Chronic diseases, median (IQR)	1.0	(0 – 1)	2.0	(1 – 3)	<0.001***
Generalized atherosclerosis ¹ , mean (SD)	1.2	(0.1)	1.1	(0.2)	<0.001**
Use of alcohol ³ , median (IQR)	0.03	(0-0.1)	0.03	(0-1.2)	0.001***
Use of benzodiazepines, n (%)	14	(6.5)	123	(33.9)	<0.001*
Smoking, n (%)					<0.001*
Never	85	(39.2)	95	(26.2)	
Former	55	(25.3)	162	(44.6)	
Current	76	(35.0)	107	(28.4)	
Neuropsychiatric characteristics					
Depression score ² , mean (SD)	27.3	(11.1)	30.0	(13)	0.01**
Apathy					
Present, n (%)	116	(53.5)	269	(74.1)	<0.001**
Total score, mean (SD)	14.3	(5.0)	17.0	(5.5)	<0.001**

Note: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

Comparison using *Chi square, **T tests or ***Mann-Whitney test.

¹Measured by the ankle-brachial index

²Measured by the Inventory of Depressive Symptomatology, 30 self-rating items

³AUDIT: Daily alcohol consumption

Table 2

Logistic regression analyses of the total group of depressed persons (n=580) with and without apathy and the effect of the interaction term age, all corrected for depression severity.

	Apathy absent n=195	Apathy present n=385	OR (95% CI) Adjusted ⁴	Wald	p- value	Interaction term age_centered p-value
Demographic characteristics						
Age in years, mean (SD)	55 (16)	62 (14)	1.03 (1.02- 1.05)	26.78	<0.001	
Female gender, n (%)	148 (76)	247 (64)	0.52 (0.35-.78)	9.99	0.002	0.6
Education, n (%)						0.6

Basic	20 (10)	67 (17)	<i>reference</i>			
Intermediate	100 (51)	214 (56)	0.79 (0.45- 1.42)	.60	0.4	0.4
High	75 (39)	104 (27)	0.52 (0.28- 0.95)	4.58	0.03	0.8
Clinical characteristics						
Chronic diseases, median (IQR)	1 (0- 2)	1 (1-3)	1.22 (1.06- 1.41)	7.71	0.005	0.98
Generalized atherosclerosis ¹ , mean (SD)	1.1 (0.15)	1.1 (0.19)	0.75 (0.25- 2.22)	0.27	0.6	0.02
Use of alcohol ³ , median (IQR)	0.03 (0- 0.4)	0.04 (0-0.5)	1.24 (0.94- 1.62)	2.33	0.1	0.6
Use of benzodiazepines, n (%)	32 (16)	105 (27)	1.63 (1.03- 2.57)	4.37	0.04	0.7
Smoking, n (%)						
Never	68 (35)	112 (29)	<i>reference</i>			
Former	65 (33)	152 (40)	1.47 (0.96- 2.28)	3.07	0.08	0.04
Current	60 (31)	119 (31)	1.9 (0.76- 1.87)	0.60	0.4	0.04
Neuropsychiatric characteristics						
Depression score ² , mean (SD)	24 (12)	31 (12)	1.05 (1.03- 1.07)	35.99	<0.001	0.8
Late life depression, n (%)	94 (48)	269 (70)	2.40 (1.66- 3.46)	21.74	<0.001	
Apathy						
Total score, mean (SD)	10 (3)	19 (4)				

Note: Data are presented as numbers (percentages), means (standard deviations) or medians (interquartile ranges), where appropriate.

¹Measured by the ankle-brachial index

²Measured by the Inventory of Depressive Symptomatology, 30 self-rating items, unadjusted

³AUDIT: Daily alcohol consumption;

⁴OR adjusted for depression severity

Table 3
Independent correlates of apathy in depressed persons (n=580)

	Multivariable analyses			
	OR	95%CI	Wald	P
Age in years	1.0	1.01-1.04	12.6	<0.001
Female gender	0.5	0.35-0.80	9.0	.003
Education	0.9	0.63-1.17	0.9	0.3
Chronic diseases	1.1	0.9-1.24	0.4	0.5

Use of benzodiazepines	1.2	0.7-1.9	0.4	0.6
Depression score	1.1	1.04-1.06	26.8	<0.001

Note: Multivariable analyses using variables (table 2) that showed a significance level of $p < 0.05$ on analyses

Depression score: Inventory of Depressive Symptomatology, 30-items self-rating

Highlights

- Apathy, as a clinically relevant syndrome, was significantly more often present in older compared to younger depressed persons.
- In both older and younger depressed persons, male gender, lower education, frequent use of benzodiazepines, chronic diseases and higher severity of depression were associated with more apathy.
- Smoking was associated with the presence of apathy in older but not in younger depressed persons.
- Age, male gender and severeness of depression were independently associated with presence of apathy in depressed persons.